**UNITED STATES DEPARTMENT OF COMMERCE**
**Patent and Trademark Offic**
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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
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| 08/954,954 | 10/21/97 | SUMMERS N | 2991/1 |

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| ART UNIT | PAPER NUMBER |
|---|---|
| 1646 | |

**DATE MAILED:** 10/13/98

**Please find below and/or attached an Office communication concerning this application or pr ceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. 08/954,954 | Applicant(s) Summers et al. |
|---|---|---|
| | Examiner Elizabeth C. Kemmerer | Group Art Unit 1646 |

☒ Responsive to communication(s) filed on *Jul 30, 1998* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) *1-22* is/are pending in the application.

Of the above, claim(s) *15-22* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-14* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims *1-22* are subject to restriction or election requirement.

**Application Papers**

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

*--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---*

## DETAILED ACTION

### *Election/Restriction*

Applicant's election with traverse of Group I, claims 1-14, in Paper No. 4 (30 July 1998) is acknowledged. The traversal is on the ground(s) that examining both groups does not pose an undue burden of examination on the Examiner. Applicant also argues that if the products recited in Group I are novel over the prior art, then the methods of Group II would also be novel. This is not found persuasive because search and examination of Group involves the extra search and examination of *ex vivo* expansion of progenitor cells, and gene therapy methods of administering cells, which is not required by the search and examination of Group I. Thus, a serious extra burden would exist if both groups were examined together.

The requirement is still deemed proper and is therefore made FINAL.

Claims 15-22 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 4.

### *Sequence Rules*

The instant application is not fully in compliance with the sequence rules, 37 CFR 1.821-1.825, because each disclosure of a sequence embraced by the definitions set forth in the rules is not accompanied by the required reference to the relevant sequence identifier (i.e., SEQ ID NO:). This occurs at least at pp. 11-12 and in Figure 5 (DNA and amino acid sequences). For sequences

disclosed in the Drawings, the sequence identifier can be referenced either in the Drawings themselves or in the relevant portions of the Brief Description of the Drawings. Also, references to GlyGlyGlySer in the text (e.g., p. 24) must be accompanied by reference to a sequence identifier

***35 U.S.C. § 112, Second Paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites a polypeptide comprising a modified EPO amino acid sequence of a particular formula. However, the recited formula is the wild type sequence, and thus it is not clear how it is modified. Also, it is not clear which numbers correspond to the C-terminus and which correspond to the N-terminus at the section of claim 1 bridging pp. 93-94. It is suggested that Applicant adopt the formula presented at p. 11 of the specification from line 4-28. The following independent claim is an example of a claim that would be free of 35 U.S.C. § 112, second paragraph, issues:

A human erythropoietin (EPO) receptor agonist polypeptide of the formula:

$$X^1\text{-}(L)_a\text{-}X^2$$

wherein:

a is 0 or 1;

$X^1$ is a peptide comprising an amino acid sequence corresponding to the sequence of residues n+1 through 166 of SEQ ID NO: 121;

$X^2$ is a peptide comprising an amino acid sequence corresponding to the sequence of residues 1 through n of SEQ ID NO: 121;

n is an integer ranging from 1 to 165; and

L is a linker.

Additionally, the abbreviation "EPO" should be spelled out in each independent claim in the interest of clarity. In claim 4, there is no antecedent basis for "the linker sequence (GlyGlyGlyGlySer SEQ ID NO: 123)" in the preceding claim 3. Also, SEQ ID NO: 123 in the sequence listing is GlyGlyGlySer, not GlyGlyGlyGlySer. In claim 12, it is not clear what the meaning of "a factor" is. Applicant may wish to consider amending "factor" to "a second protein". Claim 13 contains an improper Markush groups wherein the "and" is misplaced (it should occur in front of "multi-functional") and the plural terms should be singular. Finally, claim 14 misspells "patient".

***35 U.S.C. § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary

skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 5 and 10-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pastan et al. (U.S. Patent 5,635,599) in view of Lin (U.S. Patent 4,703,008).

Pastan et al. teach growth factor agonist polypeptides and nucleic acids encoding same, wherein the N-terminus is joined to the C-terminus directly or through a linker capable of joining the N-terminus to the C-terminus and having new C- and N-termini in the middle of the polypeptide (Fig. 1; column 2, brief description of Fig. 1; column 3, lines 35-53). Pastan et al. teach that erythropoietin (EPO) is amenable to this procedure, which they term "circular permutation" (column 4, lines 30-42). Pastan et al. teach a method of recombinantly producing the circularly permuted ligand (column 9, line 62 to column 10, line 15). Pastan et al. also tech pharmaceutical compositions comprising the circularly permuted growth factor, complementary growth factors, and a pharmaceutically acceptable carrier (columns 16-17).

Pastan et al. do not disclose a working example of circularly permuted EPO, nor do they disclose a sequence of EPO. However, human EPO had been previously characterized (Lin, Figure 9). Pastan et al. disclose that a good choice for an "opening site" (i.e., a new C- and N-termini is where substitution of amino acids is tolerated. Lin in Figure 9 align human and monkey EPO sequences. Both are functional. Differences occur at amino acid positions 25, 27, 30, 32, 80, 82, 88, 116, and 121. This suggests that an opening site would be tolerated in a circularly permuted EPO molecule at any one of these sites. Lin also teach pharmaceutical composition comprising EPO and a pharmaceutically acceptable carrier, and a method of stimulating the production of hematopoietic cells in a patient comprising administration of same (column 12).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the circularly permuted growth factors, DNA encoding same, methods of recombinantly producing same, and pharmaceutical compositions comprising same as taught by Pastan et al., and to modify that teaching by extending it to EPO disclosed by Lin, with opening sites at 25, 27, 30, 32, 80, 82, 88, 116, or 121. A reasonable expectation of success is given by Pastan et al.'s disclosure that preferred opening sites are those which can tolerate amino acid substitution and Lin's disclosure of substitution toleration at positions 25, 27, 30, 32, 80, 82, 88, 116, and 121. The motivation to do so is provided by Pastan et al. in their express suggestion to extend the teachings to EPO.

Thus, the claimed invention as a whole was very clearly *prima facie* obvious over the prior art.

*Conclusion*

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D., whose telephone number is (703) 308-2673. The examiner can normally be reached on Mondays through Thursdays from 6:30 a.m. to 4:00 p.m. The examiner can also normally be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached on (703) 308-2731.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

ECK
October 13, 1998